

### **Remarks**

Claims 1, 2, and 4-6 are currently pending in the application. In order to advance prosecution, Applicants have amended claims 1, 2, 4 and 6, and added claims 7-16. A complete listing of all the claims, in compliance with the revised amendment format, is shown above. The amendments to the pending claims are made in order to expedite the issuance of the claims. The amendments are made without prejudice, do not constitute amendments to overcome any prior art rejection, and do not present any new matter.

### **Priority**

The Office Action maintains the position that pending claims 1, 2, and 4-6 have an effective priority date of January 12, 2001. However, the Office Action correctly notes that U.S. Provisional Application No. 60/176,515 ("the '515 application") describes  $\beta$ -gal and p21 as markers. Although not acquiescing to this priority determination or the Office Action's reasoning supporting it, Applicant has amended claim 1 to recite the use of SA  $\beta$ -Gal and p21 as biological markers. Accordingly, the amended claim, and those dependant there from, are supported by the '515 application. Thus, because the reasons set forth in the Office Action no longer apply to the these claims, Applicant asserts that the priority date of the invention as presently claimed is January 12, 2000, the filing date of the '515 application, and respectfully requests the Office to accord the present claims with such a priority date.

### **Discussion of the 35 U.S.C. § 103(a) Rejections**

Claims 1 and 4 stand rejected under 35 U.S.C. § 103(a) as being obvious over Park *et al.* (Journal of Cancer Research and Clinical Oncology, 2000, Vol. 126, pp. 455-460) ("Park") in

view of Kopp *et al.* (Cancer Research, 1995, Vol. 55, pp. 4512-4515) (“Kopp”). Applicant respectfully traverses this rejection.

An analysis for obviousness requires a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue must be ascertained, and the level of ordinary skill in the pertinent art must be resolved. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). To establish a *prima facie* case of obviousness, the Office must show three basic criteria: (1) there must be a suggestion or motivation to combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) all of the claimed limitations must be taught or suggested in the combined prior art references. M.P.E.P. § 2143. The Supreme Court’s opinion in the *KSR International Co. v. Teleflex Inc.* case did not alter the basic obviousness inquiry as established by *Graham*, and, to the contrary, it reaffirmed it. The *KSR* case did reject the rigid application of the “Teaching, Suggestion, and Motivation” test, as applied by the Federal Circuit in that case, but reaffirmed the need to make the analysis explicit when articulating an obviousness rejection based on a combination of the prior art. *See KSR v. Teleflex*, 127 S. Ct. 1727, 1740 (2007), citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”)

As discussed above, claims 1 and 4, and all claims dependant there from, as amended, are entitled to a priority of January 12, 2000. Park was only received by the Journal of Cancer Research and Clinical Oncology on February 16, 2000, and accepted March 6, 2000. Therefore, the publication date of Park could not have been before March 6, 2000. As such, Park is not prior art to claims 1 and 4, as well as all claims dependant there from. Moreover, the present

Office Action has withdrawn the previous 35 U.S.C. § 102(b) rejection of claims 1, 2, and 4 as anticipated by Kopp, in apparent acknowledgement that claims 1, 2, and 4 do not teach each and every element as set forth in the claims. In view of the inapplicability of Park as prior art, and of the failure of Kopp to teach each and every element of the claims, Applicant respectfully requests withdrawal of this § 103 obviousness rejection and requests reconsideration of the claims.

Furthermore, Applicant notes that newly added claims 12-16 are not subject to this obviousness rejection. However, Applicant respectfully points out that newly added claims are directed to methods for determining a response to administration of a topoisomerase II inhibitor to an individual having breast cancer. And, at the least, neither Park nor Kopp teach the administration of topoisomerase II inhibitors to individuals having breast cancer, much less determining a response of such an administration. Therefore, neither Park nor Kopp, either alone or in combination, can anticipate or render obvious claims 12-16.

Claims 1, 2, 5 and 6 stand rejected under 35 U.S.C. § 103(a) as being obvious over Park and Kopp, and further in view of Bentsen *et al.* (U.S. 6,372,895) (“Bentsen”) and Pinkel *et al.* (U.S. 5,665,549) (“Pinkel”). Applicant respectfully traverses this rejection.

The claims as amended recite methods for determining a response to administration of a cancer chemotherapeutic agent to an individual, wherein said method comprises collecting a tissue or cell sample from an individual both before and after exposing the individual to a cancer chemotherapeutic agent, staining both samples with one or a multiplicity of stains to determine SA  $\beta$ -Gal activity, p21 expression, or both SA activity and p21 expression; measuring the optical density of the stained samples, and determining whether SA  $\beta$ -Gal activity, expression of p21 or

SA  $\beta$ -Gal activity and expression of p21 both was increased following exposure to the cancer chemotherapeutic agent.

The teaching and deficiencies, as related to the present invention, of Park and Kopp are thoroughly discussed above. As noted above, Park is not prior art to claims 1, 2, 5 and 6, or to any claims dependant there from. In addition, Applicant notes that Bentsen has a priority date of July 7, 2000, and therefore also is not available as prior art for the pending claims. The additionally cited reference, Pinkel, taken alone or in any combination with Kopp, does not teach or suggest the instantly claimed methods. Kopp is cited as teaching the measurement of TGF- $\beta$ 2 levels in a patient both before and after chemotherapeutic treatment. *See* Office Action dated April 20, 2007. As such, Kopp at the least does not teach the staining of tissue or cell samples with one or a multiplicity of stains to determine either SA  $\beta$ -Gal activity or p21 expression. The deficiencies of Kopp are not overcome by the combination with Pinkel. In this ground of rejection, Pinkel is cited additionally as teaching that an image analysis system can be used to enhance or accurately quantitate the intensity differences relative to background staining differences for more accurate and easier result interpretation. However, Pinkel does not provide any teaching whatsoever related to the staining of tissue or cell samples with one or a multiplicity of stains to determine either SA  $\beta$ -Gal activity or p21 expression. Thus, even if one skilled in the art did combine the teachings of Kopp and Pinkel, they would not have derived the presently claimed invention. Accordingly, Applicant respectfully requests withdrawal of this § 103 obviousness rejection and requests reconsideration of the claims.

Furthermore, Applicant notes that newly added claims 12-16 are not subject to this obviousness rejection. However, Applicant respectfully points out that newly added claims are directed to methods for determining a response to administration of a topoisomerase II inhibitor

to an individual having breast cancer. And, at the least, neither Park, Kopp, Bentsen, nor Pinkel teach the administration of topoisomerase II inhibitors to individuals having breast cancer, much less determining a response of such an administration. Therefore, neither Park, Kopp, Bentsen, nor Pinkel, either alone or in combination, can anticipate or render obvious claims 12-16.

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 103(a) as being obvious over Butta *et al.* (Cancer Research, 1992, Vol. 52, pp. 4261-4264) ("Butta") in view of Plant *et al.* (U.S. 5,389,523) ("Plant"). Applicant respectfully traverses this rejection.

Neither of the cited references, either alone or in combination, teach the claimed invention. Applicant notes that the newly cited references are not discussed with regard to the teaching of the other cited references, that the Office Action is thereby asserting a separate and independent ground of rejecting the pending claims for obviousness based on these references, and that the newly cited references are not being combined with the other cited references discussed above.

Butta is cited for teaching a method of determining a response to administration of a chemotherapeutic agent, tamoxifen, to human breast cancer *in vivo*. In addition, the Office Action asserts that Butta teaches that immunochemical techniques were used to measure TGF-beta expression in matched breast tumor biopsies taken from patients before and after treatment. Without acquiescing to the Office Action's characterization of Butta, Applicant notes that Butta, at the least, does not teach the staining of tissue or cell samples with one or a multiplicity of stains to determine either SA  $\beta$ -Gal activity or p21 expression. The deficiencies of Butta are not overcome by the combination with Plant. In this ground of rejection, Plant is cited additionally as exemplifying the use of ELISA as a common immunoassay format and that ELISA plates are

read by readers based on optical density measurements. Again, without acquiescing to the Office Action's characterization of Plant, Applicant notes that Plant does not provide any teaching whatsoever related to the staining of tissue or cell samples with one or a multiplicity of stains to determine either SA  $\beta$ -Gal activity or p21 expression. Thus, even if one skilled in the art did combine the teachings of Butta and Plant, they would not have derived the presently claimed invention. Accordingly, Applicant respectfully requests withdrawal of this  $\S$  103 obviousness rejection and requests reconsideration of the claims.

Furthermore, Applicant notes that newly added claims 12-16 are not subject to this obviousness rejection. However, Applicant respectfully points out that newly added claims are directed to methods for determining a response to administration of a topoisomerase II inhibitor to an individual having breast cancer. And, at the least, neither Butta nor Plant teach the administration of topoisomerase II inhibitors to individuals having breast cancer, much less determining a response of such an administration. Therefore, neither Butta nor Plant, either alone or in combination, can anticipate or render obvious claims 12-16.

Claims 1, 2, and 5 stand rejected under 35 U.S.C.  $\S$  103(a) as being obvious over *Comerci et al.* (Clinical Cancer Research, 1997, Vol. 3, pp. 157-160) ("*Comerci*") in view of *Bacus et al.* (U.S. 4,741,043) ("*Bacus*"). Applicant respectfully traverses this rejection.

Neither of the cited references, either alone or in combination, teach the claimed invention. Applicant notes that the newly cited references are not discussed with regard to the teaching of the other cited references, that the Office Action is thereby asserting a separate and independent ground of rejecting the pending claims for obviousness based on these references, and that the newly cited references are not being combined with the other cited references

discussed above.

Comerci is cited for teaching a method of determining a response to administration of a chemotherapeutic agent, beta-carotene, to human cervical intraepithelial neoplasia *in vivo*. In addition, the Office Action asserts that Comerci teaches that matched cervical biopsies taken from patients before and after beta-carotene treatment were stained simultaneously with antibodies to TGF-beta. Without acquiescing to the Office Action's characterization of Comerci, Applicant notes that Comerci, at the least, does not teach the staining of tissue or cell samples with one or a multiplicity of stains to determine either SA  $\beta$ -Gal activity or p21 expression. The deficiencies of Comerci are not overcome by the combination with Bacus. In this ground of rejection, Bacus is cited additionally as teaching the determination of optical density by image analysis. Again, without acquiescing to the Office Action's characterization of Bacus, Applicant notes that Bacus does not provide any teaching whatsoever related to the staining of tissue or cell samples with one or a multiplicity of stains to determine either SA  $\beta$ -Gal activity or p21 expression. Thus, even if one skilled in the art did combine the teachings of Comerci and Bacus, they would not have derived the presently claimed invention. Accordingly, Applicant respectfully requests withdrawal of this § 103 obviousness rejection and requests reconsideration of the claims.

Furthermore, Applicant notes that newly added claims 12-16 are not subject to this obviousness rejection. However, Applicant respectfully points out that newly added claims are directed to methods for determining a response to administration of a topoisomerase II inhibitor to an individual having breast cancer. And, at the least, neither Comerci nor Bacus teach the administration of topoisomerase II inhibitors to individuals having breast cancer, much less

determining a response of such an administration. Therefore, neither Comerci nor Bacus, either alone or in combination, can anticipate or render obvious claims 12-16.

### **Conclusion**

In view of the above amendments and remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully Submitted,

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